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SKELDING, ZACHARY S	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,346	LE GALL ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,16,17,25 and 27-31* is/are pending in the application.

4a) Of the above claim(s) *14,16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25 and 27-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks filed August 27, 2010 are acknowledged.

   Claims 1-13, 15, 18-24 and 26 have been canceled.

   Claims 14, 17, 25 and 27 have been amended.

   Claims 28-31 have been added.

   Claims 14, 16, 17, 25 and 27-31 are pending.

   Claims 25 and 27-31 are under examination wherein the elected of anti-CD3 antibody is the product of non-covalent dimerization or mutlimerization of single chain Fv antibodies wherein the antibody comprises two or more scFv antibodies wherein the Vh and Vl domains of each scFv are separated by peptide linkers or by no linkers in an orientation preventing their intramolecular pairing, i.e., the diabody format.

   Claims 14, 16 and 17 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group of invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 6, 2008.

2. The prior rejections of record can be found in the Office action mailed April 1, 2010.

   The prior rejection under 35 U.S.C. § 102(b) has been withdrawn in view of applicant's amendment to the claims.

   New Grounds of Rejection necessitated by applicant's amendments to the claims are put forth below.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

   > The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 28-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

   This is a new grounds of rejection necessitated by applicant's claim amendments.

   Claim 28 the phrase "or bound by a peptide bound characterized by the following features..." would be unintelligible to the skilled artisan. Thus, claim 28 and dependent claims thereof

are indefinite for failing to particularly point out and distinctly claim the subject matter applicant regards as the invention.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 28-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new grounds of rejection necessitated by applicant's claim amendments.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., Vas-Cath, Inc., v. Mahurkar, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116.

The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by functional characteristic, such as lacking "T cell activating properties in a peripheral blood mononuclear cell (PBMC) culture," without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest. In re Bell, 991 F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993). In re Deuel, 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995).

In the instant case, claim 28 recites a pharmaceutical composition comprising: (i) a bivalent diabody consisting essentially of a non-covalent dimer with two VH and two VL domains specific to human CD3, wherein each VH-VL pair is separated by a peptide linker or bound by a peptide bound characterized by the following features: ***…(d) it does not posses T cell activating properties in a peripheral blood mononuclear cell (PBMC) culture…***

Claim 30 recites: The pharmaceutical composition of claim 25 or 28, wherein the Vh and the VL domains of the bivalent diabody correspond to the variable domains of an antibody produced by the hybridoma of ATCC deposit number CRL 8001.

Applicant indicates on page 4 of their remarks that feature (d) of claim 28 is supported by the last paragraph of page 27 of the instant specification. The last paragraph of page 27 of the instant specification describes how PBMCs cultured with an OKT3-derived anti-CD3 diabody do not show elevated levels of the early activation marker CD25 on their cell surface.

However, the issue is that induction of CD25 is not the only marker for peripheral blood mononuclear T cell activation. Another marker for peripheral blood mononuclear T cell activation is the degree to which cells proliferate in response to the binding of anti-CD3 diabody as measured by BrdU incorporation in an autologous PBMC culture. The instant specification discloses that an OKT3-derived anti-CD3 diabody has a minor effect on T-cell proliferation in an autologous PBMC culture, see, e.g., page 25 and Figure 9, "donor A" of the instant specification.

Thus, the instant specification does not put the skilled artisan in possession of the genus of anti-CD3 diabodies lacking "T cell activating properties in a peripheral blood mononuclear cell (PBMC) culture." The sole anti-CD3 diabody exemplified by the instant specification, an OKT3-derived anti-CD3 diabody, is shown to have a minor effect on T-cell proliferation in an autologous PBMC culture. Moreover, the instant provides no direction or guidance as to what structure an anti-CD3 diabody would need have in order to "not possess T cell activating properties in a peripheral blood mononuclear cell (PBMC) culture."

Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. *See Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 ("definition by function ... does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is").

Sufficient description to show possession of such a genus "may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1567, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997). Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. *See University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 69 USPQ2d 1886 (Fed. Cir. 2004).

Moreover, according to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, especially page 1106 3rd column, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed

correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See, MPEP 2163 II.A.3a.ii.

Applicant is directed to the Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 25 and 27 stand rejected, and new claims 28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (WO 9847531) in view of Hsu et al. (Transplantation. 1999 Aug 27;68(4):545-54), Holliger et al. (5,837,242) and Chapman et al. (Nat Biotechnol. 1999 Aug;17(8):780-3), essentially for the reasons of record as put forth in the prior Office Action mailed April 1, 2010 and for the reasons given below.

Applicant puts forth a number of arguments about why they believe the claimed pharmaceutical composition is non-obvious over the applied reference teachings.

Applicant's arguments seek to establish:

(i) how the teachings of the applied references differ from the elements of the claimed invention (see 5-6 bridging paragraph – page 6, 1st paragraph of the remarks filed August 27, 2010);

(ii) why one of ordinary skill in the art would not have been motivated to combine the reference teachings (see page 6, 2nd paragraph – page 7, last paragraph);

(iii) that one of ordinary skill in the art would be more inclined to believe that an anti-CD3 diabody would have little if any effect on T cells, or possibly be even immunoactivating, and they would not be inclined to believe that an anti-CD3 diabody would be immunosuppressive due to the rigidity of an anti-CD3 diabody compared to an anti-CD3 F(ab')2 (see page 8) and (iv) demonstrate that the claimed pharmaceutical composition has an unexpectedly low ability to stimulate the proliferation of human PBMCs in culture.

Applicant's arguments have been carefully considered but have not been convincing essentially for the reasons of record as put forth in the prior Office Action and as described further below.

The claims are directed to a pharmaceutical composition comprising (i) a bivalent diabody consisting essentially of a non-covalent dimer with two VH and two VL domains specific to human CD3, wherein each VH-VL pair is separated by a peptide linker or bound by a peptide bound characterized by the following features: (a) it is devoid of constant antibody domains; (b) it specifically binds to human TCR/CD3 complex; and (c) it is capable of suppressing an immune reaction; and (ii) a suitable pharmaceutical carrier selected from the group consisting of an emulsion, a wetting agent and a sterile solution.

Starting with part (iv) of applicant's arguments, there are several issues that make the declarative evidence of Dr. Little filed August 27, 2010 in conjunction with applicant's most recent amendment and remarks insufficient to overcome the prima facie case of unpatentability.

First, the instant application puts forth a number of examples where the anti-CD3 diabody is based on the fusion of the Vh and Vl domains of the ***"OKT3" anti-CD3 antibody*** via a six amino acid linker to yield what is referred to throughout the specification as "anti-CD3 scFv6." (see, e.g., Example 1 and Figure 3 for the detailed description of this OKT3-based diabody).

Furthermore, the declaration of Dr. Little provides experimental results showing the potential of full length and F(ab')2 fragments of ***the OKT3 anti-CD3*** antibody to stimulate the proliferation of human PBMC under certain experimental conditions (see "Fig. 3").

Moreover, the declaration of Dr. Little relies on the results of Woodle et al., Transplantation. 1991 Aug;52(2):354-60, cited previously, which likewise provides experimental results showing the potential of full length and F(ab')2 fragments of ***the OKT3 anti-CD3*** antibody to stimulate the proliferation of human PBMC under certain experimental conditions, to make a point about the alleged unexpected properties of the claimed invention.

However, rather than comparing an OKT3 derived anti-CD3 diabody like that described in the instant specification to full length OKT3 and the OKT3 F(ab')2 fragment, ***the declaration instead compares a diabody having Vh and Vl domains derived from a different anti-CD3 antibody, UCHT1, to full length OKT3 and the OKT3 F(ab')2 fragment.***

This is important because it would cast substantial doubt in the mind of one of ordinary skill in the art about the significance of applicant's declarative evidence.

The skilled artisan would not assume that a diabody having Vh and Vl domains derived from the UCHT1 anti-CD3 antibody will necessarily have the same effect on human PBMC proliferation as a diabody having Vh and Vl domains derived from the OKT3 anti-CD3 antibody because the art suggests these antibodies have different biophysical characteristics.

For example, Salmeron teaches the UCHT1 anti-CD3 antibody is able to immunoprecipitate a CD3 $\varepsilon\gamma$ complex while the OKT3 anti-CD3 antibody is unable to do so, that this difference could be a function of the much lower affinity of OKT3 for CD3, and that while the UCHT1 and OKT3 anti-CD3 antibodies appear to "bind to very closely related epitopes or to overlapping ones," it is still possible that these antibodies bind different CD3 epitopes and compete for CD3-binding by some other mechanism (see Salmeron et al., J Immunol. 1991 Nov 1;147(9):3047-52 at page 3049, left col., Figure 3, and page 3051, right col., 1st paragraph).

Indeed, there are differences between the data disclosed in the instant specification which was generated with an OKT3-based diabody and the data presented in the Declaration of Dr. Little which could be the result of any of a number of variables, including the possibility of UCHT1 and OKT3 based diabodies having different effects on human PBMC proliferation.

For example, while the declaration indicates that the UCHT1 based diabody has no effect on human PBMC proliferation after 5 days in culture in the presence of 10% FCS, the instant specification shows that at least in one experiment the OKT3 based diabody induces proliferation of a human PBMC culture above background after just over 3.5 days in culture in the presence of 10% FCS. (see the instant specification at page 25 and Figure 9, "Donor A").

Thus, the skilled artisan would not be confident that the declarative evidence demonstrates an unexpected property of the claimed diabody because the skilled artisan would be very concerned that the difference between the OKT3 F(ab')2 fragment and the UCHT1 derived diabody may merely reflect their different fine specificities and biophysical characteristics rather than reflecting a special property of the anti-CD3 diabody format vs. the anti-CD3 F(ab')2 format.

Setting aside the issue of the experimental confounds raised by using anti-CD3 antibodies having different fine specificities and biophysical characteristics to attempt to demonstrate a special property of the anti-CD3 diabody format vs. the anti-CD3 F(ab')2 format, an additional concern relevant to the sufficiency of the declarative evidence as it is weighed against the prima facie case of obviousness is that several of the claims currently under examination are drawn to an anti-CD3 diabody where the Vh and Vl domains of said diabody are derived from the OKT3 antibody, not the UCHT1 antibody.

Moreover, as described above the instant specification contains extensive written description for making a diabody where the Vh and Vl domains are derived from the OKT3 antibody; however, the instant specification does not mention using the Vh and Vl domains UCHT1 to make a diabody.

As stated in MPEP § 716.06(d), "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support."

Furthermore, there is yet an additional issue with applicant's declarative evidence that should be made clear in the interest of compact prosecution.

In particular, it is the examiner's position that the data put forth in the declaration of Dr. Little would be viewed as demonstrating the inability of a UCHT1-based anti-CD3 diabody to induce the proliferation of human PBMC.

It would not be interpreted as unexpectedly showing "anti-CD3 diabody according to the above-referenced patent application exhibit[ed]…a significant immunosuppression effect" as stated in the last paragraphs of Section 5 of the Declaration. This is because Figure 3 of the declaration does not show what affect the anti-CD3 diabody may have on an immune response to an auto- or alloantigen since the PBMCs of the Figure 3 experiment are not being exposed to an auto- or alloantigen.

Indeed, applicant's attempt to show that the claimed anti-CD3 diabody has unexpectedly superior properties compared to an anti-CD3 F(ab')2 could be made much more convincing not only by demonstrating that an anti-CD3 diabody does indeed have less mitogenicity than the same anti-CD3 in a F(ab')2 format but, more importantly, that the anti-CD3 diabody is at least as immunosuppressive as the anti-CD3 F(ab')2, e.g., in a mixed lymphocyte reaction.

Notably such a showing would provide a nexus between the claimed invention "a pharmaceutical composition comprising (i) a bivalent diabody…characterized by the following features…(c) it is capable of suppressing an immune reaction…" and the immunotherapeutic uses disclosed for the claimed pharmaceutical composition (see page 16, last paragraph of the instant specification).

Put another way, to be entitled to substantial weight in the determination of obviousness, evidence of secondary considerations must be relevant to the subject matter as claimed, i.e., the strength of a showing of unexpected results is proportional to its relevance with respect to the merits of the claimed invention. See, e.g., *Ex parte Jella*, 90 USPQ2d 1009 (BPAI 2008).

As to part (i) of applicant's arguments, it is the examiner's position that applicant has mischaracterized the teachings of Smith and Woodle as well as of the instant specification.

For example, applicant argues "Woodle teaches that F(ab')2 antibodies are still capable of mediating FcR cross-linking although they are devoid of the antibody constant regions" but provides no cite for this alleged teaching and the examiner cannot find where Woodle teaches this.

Moreover, applicant misquotes Woodle at p. 356, ¶ 3, ll.8-10, "soluble F(ab')2 fragments induced minimal proliferation, suggesting that bivalent TCR crosslinking alone induced ***minimal*** T cell activation," where applicant's quote omitted the critical emphasized word.

Applicant concludes this section of their argument by stating "[h]ence, it is surprising and non-obvious that the bivalently binding anti-CD3 diabody of the present invention demonstrates a complete lack of lytic activity (see Figure 9 of the present application) while retaining the immunosuppressive properties," however the instant specification does not appear to mention lytic activity.

Moreover, it would not be accurate to say that the present invention demonstrates a complete lack of mitogenic activity because the data for at least "donor A" of Figure 9 shows otherwise (see above).

As to part (ii) of applicant's arguments, applicant argues:

"Holliger expressly teaches that 'diabodies may also bind simultaneously to two epitopes on the same surface.., by crosslinking the CD3 antigen so as to activate T-ceils,' (col. 22, ll. 13-17).

That is, Holliger also teaches T cell activation by an antibody devoid of constant regions. 'T cell activation' is generally considered in the art as a stimulation of T lymphocytes to undergo mitosis, and increased lymphokine production and cytotoxic cell activity (see Smith, p. 24, 1.24 thru p. 26, 1.9). On the other hand, the intended 'immunosuppression' effect according to the present invention relates to the prevention of T lymphocyte activation (see p. 9, ¶ 3 of the specification). Thus, the T cell activation mentioned by Holliger is exactly the opposite of the intended effect of the present invention.

Because the generally accepted meaning of T cell activation is lytic and mitogenic activities induced by stimulated T cell receptors, one skilled in the art would understand Holliger's reference to T-cell activation as meaning that their propensity for cytolytic or mitogenic activity would be stimulated by diabodies. Holliger does not teach or suggest whether diabodies can inhibit T cell proliferation. Also the lack of antibody constant regions in the diabodies does not indicate that immunogenic reactions can be avoided, as Woodle teaches that F(ab')2 antibodies devoid of FcR binding constant regions can still induce some T cell activation by TCR cross-linking. Therefore, one skilled in the art would not have had a reasonable expectation of success that an anti-CD3 diabody lacking lyric and mitogenic activity can be made. Considering the T cell activating function of diabodies suggested by Holliger, one skilled in the art, when faced with the problem of making low mitogenic

antibodies, would not have had any incentive to replace Smith's anti-CD3 F(ab')2 with an anti-CD3 diabody."

This is similar to applicant's previous argument (see remarks filed January 7, 2010 at page 6) and it remains the examiner's position that applicant is narrowly construing the teachings of Holliger to fit their argument rather than considering them through the lens of one of ordinary skill in the art as of applicant's date of invention.

The teachings of Holliger applicant refers to in their argument above are reproduced below: "The diabodies may also bind simultaneously to two epitopes on the same surface, for example a viral coat, so as to bind with high avidity and to block the uncoating of the virus; or by cross-linking the CD3 antigen so as to activate T-cells." (see Holliger at col. 22, 1st paragraph).

One of ordinary skill in the art would understand this teaching to mean that an anti-CD3 diabody by cross-linking CD3 molecules on the surface of a T cell can activate said T cell.

As put forth in the previous Office Action mailed July 9, 2009 at page 4, 5th paragraph, in the context of the teachings of Smith the ability of an anti-CD3 antibody to cross-link two CD3 molecules on the T-cell surface and deliver a partial signal, i.e., a partial activation, was known to be essential for its ability to immunomodulate the Th1/Th2 cytokine balance in favor of Th2.

Thus, one of ordinary skill in the art would not consider the teachings of Smith and Holliger to be inconsistent as implied by applicant's argument. Rather one of ordinary skill in the art would consider Holliger as teaching that a CD3 diabody can bind simultaneously to two epitopes on the surface of a T cell so as to activate said T-cell, a function consistent with the ability of other antibodies that cross-link CD3 on the surface of a T cell and lack an Fc region, such as an OKT3 F(ab')2 fragment, to do the same.

With respect to how one of ordinary skill in the art would consider the teachings of Smith and Holliger, applicant further argues: "In the present Office Action, the Examiner puts forth that the teachings of Holliger and Smith would be consistent (p. 4, ¶ 3). However, the immunomodulation of T cells by the non-Fc binding anti CD3-IgG3 antibody to which the Examiner is referring is not the general suppression of T cell activation due to down-modulation (or disappearance) of the TcR. Smith teaches that the antibody which has low affinity FcR binding activity delivers a partial T cell signal which promotes Th2 cell proliferation and suppression of Th1 cell responses (e.g., p. 18, 11.23-28) and as such, its action may be fairly complex. That is, Smith teaches a selective T cell activation that contributes to the immunosuppressive activity (e.g., p. 4, ¶ i), which immunomodulation has to be distinguished from the general immunosuppression by inducing the internalization and disappearance of the TcR as shown by the anti-CD3 diabodies according to the present invention (see Example 9). As such, the possibility of T cell activation mentioned by Holliger points away from suppressing T cell activation by inducing the internalization and

disappearance of the TcR. In fact, Holliger does not suggest such immunosuppressive properties. Holliger's teaching that cross-linking the CD3 antigen activates T-cell would not be considered by one skilled in the art as a function consistent with suppressing T cell activation by inducing internalization and disappearance of the TcR that is intended by the present invention."

Applicant's arguments and assertions have been considered but have not been found convincing for a variety of reasons.

First, it should be noted that while Smith does teach the low FcR affinity anti-CD3 IgG3 antibody delivers a partial T cell signal which promotes Th2 cell proliferation and suppression of Th1 cell responses, Smith also teaches "Previous studies have shown that treatment of T cells with anti-CD3-IgG3 resulted in down-modulation of TCR expression within 24 hours (Alegre, 1993)." (See page 91, 2nd paragraph).

Furthermore, Smith teaches the following at page 50, 2nd paragraph "F(ab')2 fragments of OKT3 have led to potent immunosuppression and TCR modulation, in vitro."

Thus, from the teachings of Smith one of ordinary skill in the art would appreciate that antibodies which deliver a partial T cell signal which promotes Th2 cell proliferation and suppression of Th1 cell responses ***can also*** simultaneously induce TCR down-modulation, i.e., the internalization and disappearance of the TcR.

Therefore, in contrast to applicant's arguments, Holliger teaching that "diabodies may also bind simultaneously to two epitopes on the same surface, for example a viral coat, so as to bind with high avidity and to block the uncoating of the virus; or by cross-linking the CD3 antigen so as to activate T-cells" does not "points away from suppressing T cell activation by inducing the internalization and disappearance of the TcR" when the combined teachings of Smith and Holliger are considered through the lens of one of ordinary skill in the art as of applicant's date of invention.

Secondly, even if, arguendo, the combined teachings of Smith and Holliger failed to teach an antibody capable of bivalent CD3 binding on the cell surface was capable of inducing TCR down-modulation, this would not negate the prima facie case of obviousness because as stated in MPEP § 2144, "The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005) ('One of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings.'); *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972) (discussed below); *In re Dillon*, 919 F.2d 688, 16

USPQ2d 1897 (Fed. Cir. 1990), *cert. denied*, 500 U.S. 904 (1991) (discussed below)...The court held 'it is not necessary in order to establish a *prima facie* case of obviousness . . . that there be a suggestion or expectation from *the prior art* that the claimed [invention] will have the same or a similar utility as *one newly discovered by applicant*,' and concluded that here a *prima facie* case was established because '[t]he art provided the motivation to make the claimed compositions in the expectation that they would have similar properties.' 919 F.2d at 693, 16 USPQ2d at 1901 (emphasis in original)."

Further along these lines MPEP § 2145 instructs, "'The fact that appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious.' *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985)"

As to part (iii) of applicant's arguments, applicant argues one of ordinary skill in the art would be more likely to believe an anti-CD3 diabody would bridge two T cells having CD3 molecules than bind two CD3 molecules on the same cell surface. Applicant further posits that if an anti-CD3 diabody were to form an intermolecular interaction between T cells, then the T cells should behave in a similar way as do T cells crosslinked to B cells by the anti-CD3 x anti-CD19 diabody exemplified by the teachings of Kipriyanov et al., 1999.

Applicant's arguments and assertions have been considered but have not been found convincing.

First, one of ordinary skill in the art would recognize that an important difference between the anti-CD3 x anti-CD19 diabody of Kipriyanov, and an anti-CD3 x anti-CD3 diabody is that CD19 is not expressed by T cells. Thus, the anti-CD3 x anti-CD3 diabody possesses the ability to crosslink two CD3 molecules on the same cell surface unlike the anti-CD3 x anti-CD19 diabody.

Secondly, while applicant's argument that the anti-CD3 diabody has a rigid rod like structure compared to the F(ab')2 is acknowledged, applicant has not provided sound scientific reasoning or objective evidence to support their argument that such a structure would preclude the side-by-side interaction of CD3 epitopes on the same surface as taught by Holliger.

In this regard it is noted that the arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., *In re Huang*, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984), See MPEP § 2145.

In conclusion, when Applicant's arguments, the teachings of the instant specification and the Declarative evidence of Dr. Little are taken as a whole and weighed against the evidence supporting the *prima facie* case of unpatentability, the instant claims, by a preponderance of evidence, remain unpatentable. See M.P.E.P. § 716.01(d).

9. Claims 29 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (WO 9847531) in view of Hsu et al. (Transplantation. 1999 Aug 27;68(4):545-54), Holliger et al. (5,837,242) and Chapman et al. (Nat Biotechnol. 1999 Aug;17(8):780-3) as applied to claims 25 and 27, 28 and 30 above, and further in view of Kipriyanov et al. (Protein Eng. 1997 Apr;10(4):445-53), essentially for the reasons of record as put forth in the Office Action mailed October 3, 2008 at page 10, Section 12.

Applicant argues Kipriyanov describes an OKT3 scFv using the 17 amino acid linker AKTTPKLEEGEFSEARY and that Holliger teaches the use of linkers consisting of 10, 15 or longer amino acids, and that said teachings point to linkers longer than the 6 amino acid SEQ ID NO: 1. Applicant further asserts that the serine mutation would not have been obvious because the combination of the base references - Smith, Hsu, Holliger and Chapman was allegedly not obvious.

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record put forth in the Office Action mailed April 1, 2010 and the reasons of record put forth in the Office Action mailed October 3, 2008 at page 10, Section 12.

As stated in the Office Action mailed October 3, 2008 at page 10, Section 12, Holliger teaches "[w]here one is seeking to convert a particular cloned antibody into a diabody format, it is a simple matter to vary the linker length (e.g. from 0 upwards) to see what works best. Likewise, substitution of different linkers, even of the same length, may be advantageous." (see Holliger column 16, 2nd paragraph).

In this regard, Holliger teaches that linkers of length anywhere from 0-9 amino acids allow for the production of diabodies although linkers of 10 amino acids or more can be used if they are subject to "limiting structural features" which serve to decrease their effective length (see Holliger, e.g., column 3, 5th paragraph). Holliger further teaches that one source of starting material for a diabody is a cloned scFv (see Holliger, e.g., column 3, 5th paragraph; column 27, 5th paragraph and Example 1, columns 31-35).

Given the reference teachings, in contrast to applicant's argument, one of ordinary skill in the art would have been motivated to merely shorten the linker already present in the anti-OKT3 scFv of Kipriyanov to generate an anti-CD3 diabody because such a modification would not have required the additional complication of introducing structurally constraining residues which would be required to use the longer linkers contemplated by Holliger.

In following the teachings of Holliger to make a diabody from the scFv of Kipriyanov, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have had a reasonable expectation of successfully using any one of a finite number of possible, and equally reasonable, up to 9 amino acid linker sequences derived from the 17 amino acid linker AKTTPKLEEGEFSEARY to make an anti-CD3 diabody, the linker of

SEQ ID NO: 1 being one possibility (S from the OKT3 Vh C terminal amino acid + AKTTPK).

Furthermore, with respect to preparing an OKT3 based diabody comprising a serine mutation at Kabat position H100A in place of the Cys found in the parent antibody, one of ordinary skill in the art would have been motivated to make such a change given the teachings of Kipriyanov that this particular substitution increases bacterial production of an OKT3 scFv without adversely affecting CD3 binding.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. Claims 25 and 27 stand rejected and new claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Holliger (5,837,242), essentially for the reasons of record as put forth in the Office Action mailed April 1, 2010 as described further below.

Applicant argues the teachings of Holliger do not render the claimed invention obvious because Holliger teaches CD3 cross-linking activates T cells, and "[t]herefore, one skilled in the art would not have had a reasonable expectation of success from the teaching of Holliger that a pharmaceutical composition comprising a bivalent, dimeric anti-CD3 diabody can be used for immunosuppression." (see remarks at page 12, 6th paragraph).

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed April 1, 2010.

Holliger need not teach that a pharmaceutical composition comprising an anti-CD3 diabody which cross-links CD3 on the surface of a cell and activates CD3 can act as an immunosuppressant because this is property is inherent to a pharmaceutical composition comprising an anti-CD3 diabody.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. No claims are allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachary Skelding/
Primary Examiner, Art Unit 1644